

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/IB2018/053908	International filing date (day/month/year) 31.05.2018	Priority date (day/month/year) 02.06.2017
International Patent Classification (IPC) or both national classification and IPC INV. C07K16/28 A61P35/02		
Applicant PFIZER INC.		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Telephone No. +49 89 2399-0 
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 4, 8(completely); 1-3, 5-7, 9-28(partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☒ no international search report has been established for the whole application or for said claims Nos. 4, 8(completely); 1-3, 5-7, 9-28(partially)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).
- ☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-3, 5-7, 9-28(all partially)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement
- | | | |
|-------------------------------|-------------|--------------------------------------|
| Novelty (N) | Yes: Claims | <u>1-3, 5-7, 9-28(all partially)</u> |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | <u>1-3, 5-7, 9-28(all partially)</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-3, 5-7, 9-28(all partially)</u> |
| | No: Claims | |
2. Citations and explanations
- see separate sheet**

Re Item IV

Lack of unity of invention

- 1 This Authority considers that the application does not meet the requirements of unity of invention and that there are 33 inventions.
 1. claims: 1-3, 5-7, 9-28(all partially)
Subject-matter of claims 1 to 3, 5 to 7 and 9 to 28 as far as the antibody has the CDRs of the antibody P4F6.
 - 2-32. claims: 1-3, 5-28(all partially)
Subject-matter of claims 1 to 28 as far as the antibody has the CDRs of the antibodies P4C7, P3A1, P5A3, P9B5, P9F1, P1B4, P1B11, P7H3, P3E10, P1A5, P5F7, P4H11, P15F7, P12B6, P8B6, P14G2, P7F9, P08B06EE, P04A04, P01A05, P08B03, P5F7g, P10A02g, P10A04g, P10A05g, P10A07g, P10B03g, P10B06g, P5F7g2, P5F7g3 and P5F7g4. Each of the 31 antibodies defines a separate invention.
 33. claims: 4(completely); 9-28(partially)
Bispecific antibody according to claim 4 and subject-matter of claims 9 to 28 as far as it refers to said bispecific antibody.
- 1.1 The reasons, for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:
 - 1.1.1 According to Rule 13.1 PCT, an international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art (Rule 13.2 PCT).
 - 1.1.2 Inventions 1 and 33 share the technical feature of being related to antibodies specifically binding FLT3.

Many antibodies against FLT3 have been identified in the art:

- D1 identifies a number of antibodies specifically binding FLT3 (see D1: the examples, the claims). The epitopes are either in the domain 2 region (E3 binders) or before the domain 1 region (E1 Binders) (see D1: the examples, in particular Table 2 for the identification of the region bound by the antibodies). A number of bispecific anti-FLT3/CD3 antibodies were generated and found to be cytotoxic (i.e. suitable to redirect effector T cells against FLT3-expressing target cells). The antibodies of D1 bind to both human and macaque FLT3 (see D1: examples 5 and 6).
- D2 identifies three antibodies specifically binding FLT3 (see D2: the examples, the claims). The antibodies bind either domain 4 or domain 5 (see D2: page 14, left-hand column, paragraph [0136]).
- D3 discloses bispecific anti-FLT3/CD3 antibodies based on the anti-FLT3 antibodies 4G8 and BV10 which bind domain 4 and domain 2, respectively (see D3: the examples, page 5, lines 27 and 28; SEQ ID NO: 1, 2, 5 and 6).
- Bispecific anti-FLT3/CD3 antibodies based on the anti-FLT3 antibodies 4G8 and BV10 are also disclosed in D4 (see D4: the examples; Figure 6).
- D5, in the context of the construction of CAR molecules, discloses the sequence of two particular anti-FLT3 antibodies, FLT3-1 and FLT3-2 which seem to correspond to or be derive from 4G8 and BV10 (see D5: the abstract, Tables 1 and 2) and mentions a large number of commercially available alternatives (see D5: page 50, paragraph [0169]).
- D6 discloses the isolation of an anti-FLT3 antibody, v62-1b21, and the use thereof to generate antibody drug conjugates (see D6: the examples). This antibody does not compete with the FLT3 ligand (see D6: example 14).

Therefore, the technical feature of being related to antibodies specifically binding FLT3 is clearly not novel in view of D1 to D5 and cannot correspond to a special technical feature in the sense of Rule 13 PCT.

Antibodies merely defined structurally by their CDRs do not have quantitatively any inherent feature (e.g. a particular affinity). Therefore, such aspects cannot correspond to special technical features in the sense of Rule 13.2 PCT.

Binding to a particular domain of FLT3 as long as this is not associated to a surprising effect, is also not considered as a special technical feature in the sense of Rule 13.2 PCT (see the present application: Table 6). In addition as noted above, the antibody 4G8 of the prior art binds to domain 4 and has been used to generate bispecific antibodies targeting FLT3 and CD3 in D3 and D4.

In the same way, a high level of sequence identity is not considered to correspond to a special technical feature in the sense of Rule 13 PCT in absence of evidence that this is associated with an inherent surprising effect.

In absence of evidence that two or more of the 32 antibodies forming the basis of the present inventions share technical features which would be novel and inventive other the disclosures of D1 to D6 (including the commercially available antibodies listed in D5), it is considered that there is no special technical features in the sense of Rule 13.2 PCT linking any of the inventions 1 to 32.

- 1.1.3 Taking any of D1 to D6 as closest prior art, inventions 1 to 32 solve the problem of providing alternative anti-FLT3 antibodies.

The solution to this problem is for each invention one of the 32 antibodies identified above.

As discussed above, there is no technical relationship among these antibodies involving one or more of the same or corresponding special technical features.

Taking D1, D3 or D4 as closest prior art, invention 33 solves the problem of providing alternative bispecific antibodies suitable to redirect effector cells to cells expressing FLT3

The solution to the problem is the bispecific antibody of claim 4 which has a particular format (full-length antibody). This aspect is unrelated to the solutions of inventions 1 to 32. In addition, it is again noted that antibodies binding to domain 4 of human FLT3 are already disclosed in D2 to D4 (see above). Therefore, this aspect cannot correspond to a special technical feature linking invention 33 to some of the inventions 1 to 32.

- 1.1.4 Consequently the application does not meet the requirement for unity of invention (Rule 13 PCT) and corresponds to 33 inventions.
- 1.1.5 It is noted that the number of inventions has been restricted according to the antibodies which potentially have a basis in the application (see the present application: Tables 1 and 2) and which comprise all the essential technical features of a structurally defined antibody (i.e. at least 6 defined CDRs; Article 6 PCT).

The first invention has been defined based on the first sequences mentioned in claim 1 which would allow to define an antibody with all its essential technical features, namely the sequences SEQ ID NO: 37/38/39; SEQ ID NO: 40/41; SEQ ID NO: 42; SEQ ID NO: 144; SEQ ID NO: 145; SEQ ID NO: 146 which correspond to the CDRs of the antibody P4F6.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Invention 1: claims: 1-3, 5-7, 9-28(all partially)

Subject-matter of claims 1 to 3, 5 to 7 and 9 to 28 as far as the antibody has the CDRs of the antibody P4F6

2 As far as it belongs to invention 1, the subject-matter of claims 1 to 3, 5 to 7 and 9 to 28 is considered to be novel because none of the antibodies of the prior art has the corresponding combination of CDRs.

3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 3, 5 to 7 and 9 to 28 does not involve an inventive step in the sense of Article 33(3) PCT.

3.1 Claim 1

Any of D1 to D6 can be considered as closest prior art. D1 is used in the reasoning below. D1 discloses a number of anti-FLT3 antibodies and the use thereof to generate bispecific antibodies targeting FLT3 and CD3 (see D1: the examples).

The antibody of claim 1 as far as it belongs to invention 1 differs from the antibodies of D1 in that it has a different set of CDRs.

The functional consequence of this difference is that it binds to a different epitope. In absence of evidence showing that the binding to a different epitope allows to solve a concrete technical problem, the objective technical problem can be formulated as the provision of an alternative anti-FLT3 antibody.

The provision of alternative anti-FLT3 antibodies is considered to be pure routine. The arbitrary selection of a particular antibody among all possible antibodies cannot involve an inventive step. Therefore, the antibody of claim 1 does not involve an inventive step.

3.2 Claim 2

The antibody of claim 2 as far as it belongs to invention 1 has additional inherent functional features, including a particular affinity as shown in Table 6 of the present application. However, this affinity does not represent an improvement over the antibodies of D1 (see D1: Tables 3a and 3b). Therefore, the same reasoning as above applies *mutatis mutandis*.

3.3 Claim 3

The same reasoning as for claim 1 applies *mutatis mutandis*.

3.4 Claims 5 to 10

Claims 5 to 10 are directed to bispecific antibodies having a particular format and suitable to redirect T-cells to cancer cells expressing FLT3, in particular bispecific antibodies targeting FLT3 and CD3. D1 is also directed to bispecific antibodies targeting FLT3 and CD3 but uses a different format (see D1: the examples). The particular format of the present claims including the mutations listed in claims 9 and 10 is already known in the art in the context of antibodies having the same general purpose (i.e. redirecting T cells to cancer cells) (see D7: example 8 and claims 33 and 34). Thus, it is considered that the choice of the format in claims 5 to 10 does not involve an inventive step.

Therefore, claims 5 to 10 are considered to lack an inventive step.

3.5 Claims 11 to 28

Claims 11 to 28 correspond to trivial aspects or to obvious medical uses for anti-FLT3 antibodies and/or bispecific anti-FLT3/CD3 antibodies (see D1: claims 18 to 20; page 87, last paragraph to page 88, paragraph 2; D2: claims 21 to 24; page 12, left-hand column, paragraph [0125]; D3: page 24,

paragraph [0122]; D4: claims 50 to 52; page 52, paragraph [00133]; D6: claims 27 to 33; page 90, paragraph [0326] to page 96, paragraph [0349]). Therefore, claims 11 to 28 do not involve an inventive step.

- 4 The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment (or the corresponding method; see present claims 16 and 18 to 27), but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.
- Patentability, in particular novelty and inventive step, of claims 14 and 15 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.